

PRE-CLINICAL RESEARCH

Noninvasive Renal Sympathetic Denervation by Extracorporeal High-Intensity Focused Ultrasound in a Pre-Clinical Canine Model

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Objectives	This study investigated the feasibility of noninvasive renal sympathetic denervation (RSD) by using the novel approach of extracorporeal high-intensity focused ultrasound (HIFU).
Background	Catheter-based RSD has achieved promising clinical outcomes.
Methods	Under the guidance of Doppler flow imaging, therapeutic ablations (250 W × 2 s) were performed by using extracorporeal HIFU on the bilateral renal nerves (36.3 ± 2.8 HIFU emissions in each animal) in a mean 27.4-min procedure in 18 healthy canines of the ablation group. Similar procedures without acoustic energy treatment were conducted in 5 canines of the sham group. The animals were killed on day 6 or 28. Blood pressure (BP), plasma noradrenaline (NA) level, and renal function were determined on days 0, 6, and 28. Pathological examinations were performed on all retrieved samples.
Results	All of the animals survived the treatment. After ablation, BP and NA significantly decreased compared with the baseline values (BP changed −15.9/−13.6 mmHg, NA changed −55.4% [p < 0.001] 28 days after ablation) and compared with the sham group on days 6 and 28. Ablation lesions around the renal artery adventitia were observed on day 6. A histological examination revealed the disruption of nerve fibers, necrosis of Schwann cells and neurons, and apparent denervation on day 28. No procedure-related complications were observed.
Conclusions	Effective RSD was successfully achieved by using the extracorporeal HIFU method in canines. Thus, noninvasive HIFU may be further explored as an important and novel strategy for RSD. (J Am Coll Cardiol 2013;61:2185–92) © 2013 by the American College of Cardiology Foundation

It is estimated that 1 billion individuals worldwide suffer from hypertension, and hypertension-related complications are recognized as the major cause of morbidity and mortality

(1). Recently, a catheter-based strategy for renal sympathetic denervation (RSD) was developed for the management of drug-resistant hypertension, and it has achieved encouraging clinical outcomes (2). The therapeutic benefits of RSD have also been shown for those diseases associated with sympathetic overactivity, such as insulin resistance, arrhythmia, and heart failure (3,4). However, intervention-related complications can occasionally occur. In addition, vascular wall injury has been observed in a pre-clinical model (5), and hemodynamic stenosis has been found in clinical case reports, possibly due to related complications (6). Many new devices are currently under investigation, such as chemical renal denervation using a drug delivery approach with a sidehole balloon catheter, which may help to reduce the potential damage to the artery wall (7).

High-intensity focused ultrasound (HIFU) has been used to noninvasively ablate tissue by extracorporeally delivering focused acoustic energy. This technique is considered the

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Abbreviations and Acronyms

BP	= blood pressure
BUN	= blood urea nitrogen
CDFI	= color Doppler flow imaging
HIFU	= high-intensity focused ultrasound
NA	= noradrenaline
Na⁺	= sodium
RSD	= renal sympathetic denervation
sCr	= serum creatinine

ideal source of energy, especially for the ablation of deep solid tissue (8). It has also been clinically used to treat uterus, kidney, and liver tumors (9,10). In addition, the application of HIFU has been expanded significantly in recent years (11,12).

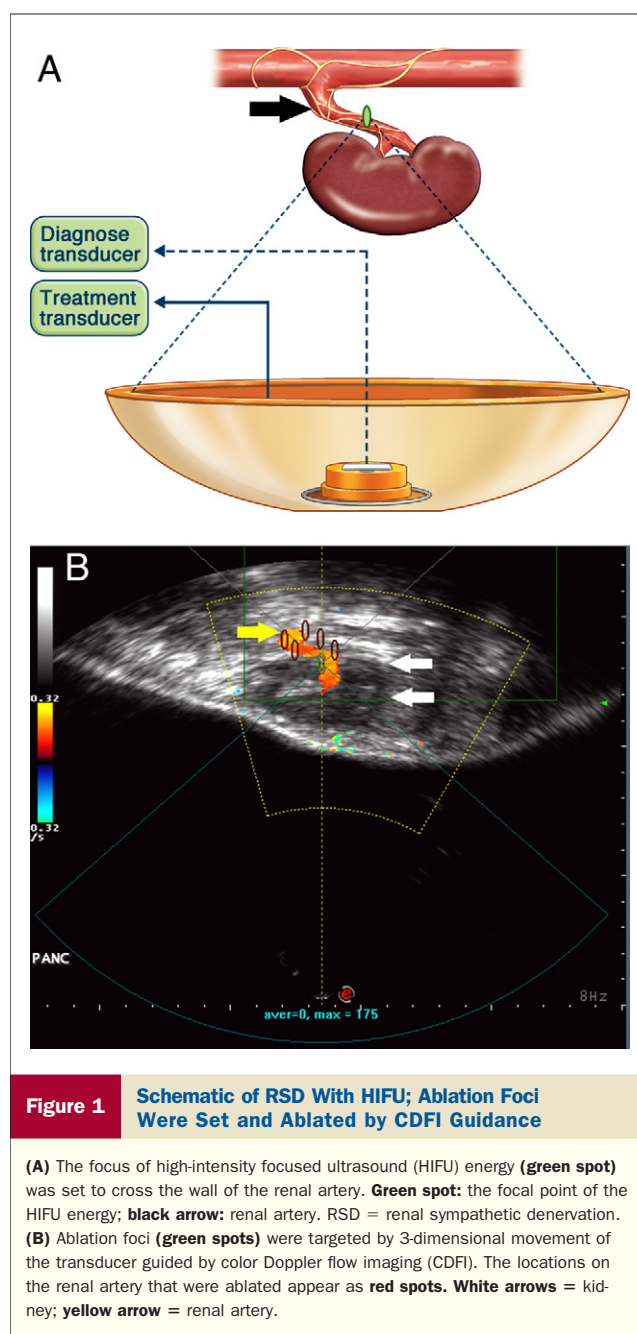
To the best of our knowledge, few studies have reported the use of noninvasive HIFU for RSD. The current study was designed to explore the possible use of this new technique for RSD in a canine model by investigating the feasibility and safety associated with this procedure.

Methods

HIFU system for RSD. The HIFU tumor therapeutic system (Model-JC200, certified by the European Union, Chongqing Haifu Technology Co. Ltd., Chongqing, China) was used. The therapeutic focused ultrasound beam was produced by a 220-mm spherically curved therapeutic transducer with focal length of 132 mm. The physical focal region was ellipsoid and $<2 \times 2 \times 6 \text{ mm}^3$. The operating frequency was 0.98 MHz (corresponding to 1.58-mm wavelength). The acoustic power of the therapeutic transducer ranged from 33 to 550 W, with an acoustic intensity at focus from 467 to 7,785 W/cm² under a degassed water acoustic environment. A diagnostic probe was aligned coaxially to the therapeutic transducer to locate the target tissues. By adjusting the transducer in 3 dimensions, the focus could be moved 1 mm by 1 mm to target the renal artery.

Animal preparation. The experimental protocol was approved by the Institutional Ethics Committee of Chongqing Medical University. The use and care of the animals were in compliance with the U.S. National Institutes of Health Guide for Care and Use of Laboratory Animals.

Twenty-three healthy mongrel canines (15 to 20 kg, purchased through the Experimental Animal Care Center of Chongqing Medical University) of either sex were distributed randomly into an ablation group ($n = 18$) and a sham group ($n = 5$). All of the canines were anesthetized with 3% pentobarbital sodium (30 mg/kg) intraperitoneally. The abdominal fur along the acoustic path was removed, and the skin was degassed with 75% alcohol and suctioned for degassing. The right femoral artery was punctured, and a syringe attached to a pressotransducer (Model YPJ01, Chengdu Instrument Factory, Chengdu, China) temporarily for every invasive blood pressure (BP) measurement. BP was recorded with a RM6240 Physiology Signal Collection Processing System (Chengdu Instrument Factory) before ablation (defined as baseline).



At days 6 and 28 post-ablation, the follow-up study used a similar procedure to measure BP, which was recorded 30 min post-anesthesia.

HIFU ablation procedure for RSD. In the ablation group, the left abdominal wall of each canine was immersed in the therapeutic chamber filled with degassed water, which provided acoustic coupling between the transducer and skin (13). Color Doppler flow imaging (CDFI) on the long-axis view of the left renal artery was obtained by adjusting the relative positions of the transducer and animal (Fig. 1A). Using CDFI as a guide, the foci of the extracorporeal HIFU were set on the zygomorphic wall at the proximal, middle, and distal right renal artery, respectively.

Therapeutic ablations ($250\text{ W} \times 2\text{ s}$) were performed at each set of foci. A total of 6 emissions of acoustic power were delivered when every segment of the renal artery was visible on an ultrasonographic view (Fig. 1B). The therapeutic transducer was moved 2 mm dorsally or ventrally to initiate the viewing of the next set of ablations. In each visual field, the focus locations and power emissions were guided by using CDFI. For example, there were 2 emissions of acoustic delivery if the ultrasonographic view could only provide the proximal segment, and the deliveries of acoustic energy were not finished until the CDFI of the renal artery disappeared. The same procedure was subsequently performed on the right renal artery. In the sham group, 5 canines underwent a similar procedure without the delivery of acoustic energy. The procedure time, defined as the duration when the animal was immersed in the therapeutic chamber until the bilateral renal nerve had been ablated, was recorded for every animal.

Post-ablation procedure. All animals received standard care. In the ablation group, the canines were killed on day 6 ($n = 10$) or day 28 ($n = 8$) post-ablation by intravenous injection of 10% potassium chloride after BP was measured invasively. The tissues along the acoustic path and near the foci, including the abdominal wall, kidney, spleen, ureters, intestinal tract, liver, and target renal artery, were retrieved for gross and histological examination. In the sham group, BP was also measured on days 6 and 28, and the histological examination was performed on day 28.

Renal function and sympathetic activity detection. The plasma noradrenaline (NA) concentration was measured by using a commercially available radioimmunoassay kit (Labor Diagnostika Nord GmbH & Co. KG, Nordhorn, Germany) (14). Blood urea nitrogen (BUN), serum creatinine (sCr), and serum sodium (Na^+) were measured by using a standard procedure before ablation and on days 6 and 28.

Statistical analysis. Changes in BP, NA, BUN, sCr, and Na^+ values were analyzed from baseline to 6 or 28 days by using analysis of variance models for completely randomized and for repeated measure designs. $p < 0.05$ was considered statistically significant. The data are presented as the mean \pm SD or percent change. All statistical analyses were performed by using SAS version 9.3 (SAS Institute Inc., Cary, North Carolina).

Results

Overall procedural considerations. CDFI of the targeted renal artery was acquired in all experimental canines. In this study, 3 to 5 CDFI-guided ultrasonographic views of the renal arteries were obtained in each unilateral renal artery, although some views only showed segmental vessels. The total mean HIFU ablation was 36.3 ± 2.8 emissions for the RSD of each pair of renal arteries, and the procedure time was 27.4 ± 3.7 min.

BP measurement. On days 6 and 28 post-ablation, systolic BP (12.3 and 15.9 mm Hg on days 6 and 28; both $p < 0.001$) and diastolic BP (11.6 and 13.6 mm Hg on days 6 and 28; both $p < 0.001$) significantly decreased relative to the individual baseline BP (Fig. 2A). Similarly, after ablation, the BP in the ablation group was significantly lower than that of the sham group on both days.

In the sham group, at baseline and the 6- and 28-day follow-up, BP had not significantly changed (Table 1).

Renal functions and sympathetic activity detection. On day 6 post-ablation, NA was reduced by 50.1% ($p < 0.001$), but BUN, sCr, and Na^+ were not significantly different from baseline levels. However, both NA (55.4%; $p < 0.001$) and Na^+ (4.5%; $p = 0.007$) were reduced on day 28 post-ablation; BUN and sCr were not significantly different from baseline (Fig. 2B). Meanwhile, NA and Na^+ in the ablation group were significantly lower than that of the sham group on day 28.

In the sham group, at baseline and the 6- and 28-day follow-ups, there were no significant differences among NA, BUN, sCr, or Na^+ (Table 1).

Gross and histological evaluation. In the ablation group, a gross examination revealed the presence of several hemorrhagic spots on the fatty tissue around the target renal arteries in a diffused or clustered distribution pattern on day 6. After removing the fatty tissue layer, ablation lesions were also found on the renal artery adventitia, and some lesions were clustered around the nerve fibers (Fig. 3A). On day 28, the slightly yellow fatty tissue was adhered to the target regions, although the lesions of the fatty tissue were gone (Fig. 3B).

A histological evaluation showed the vacuolar change of the target nerve fibers and a change of the interstitium to a mildly myxoid phenotype on day 6. The nuclei of the Schwann cells were darkly stained and exhibited pyknosis or karyorrhexis, or were even absent (Figs. 4A and 4B). The distal regions of the target lesions showed ganglion-like degeneration, swelling of the perikaryon, eosinophilic enrichment, and, in some cases, the disappearance of Nissl bodies.

On day 28, the target nerve fibers appeared shrunken and vacuolated. Necrosis of the Schwann cells was also observed around the targeted area. The myxoid change of the nerve fibers was more apparent than on day 6 (Figs. 4C and 4D). In the sham group, the histological findings remained unchanged.

Safety considerations. The vital signs of all canines were normal during the procedure and post-ablation. All of the canines survived the treatment until they were killed. The gross and histological evaluations did not reveal significant injuries along the acoustic path, including the skin, liver, spleen, kidney, ureters, intestinal tract, and the tissue around the target region.

The targeted renal arteries were smooth and had an intact vascular wall and endothelium. The ablation lesions were only found on the adventitia and immediately surrounding

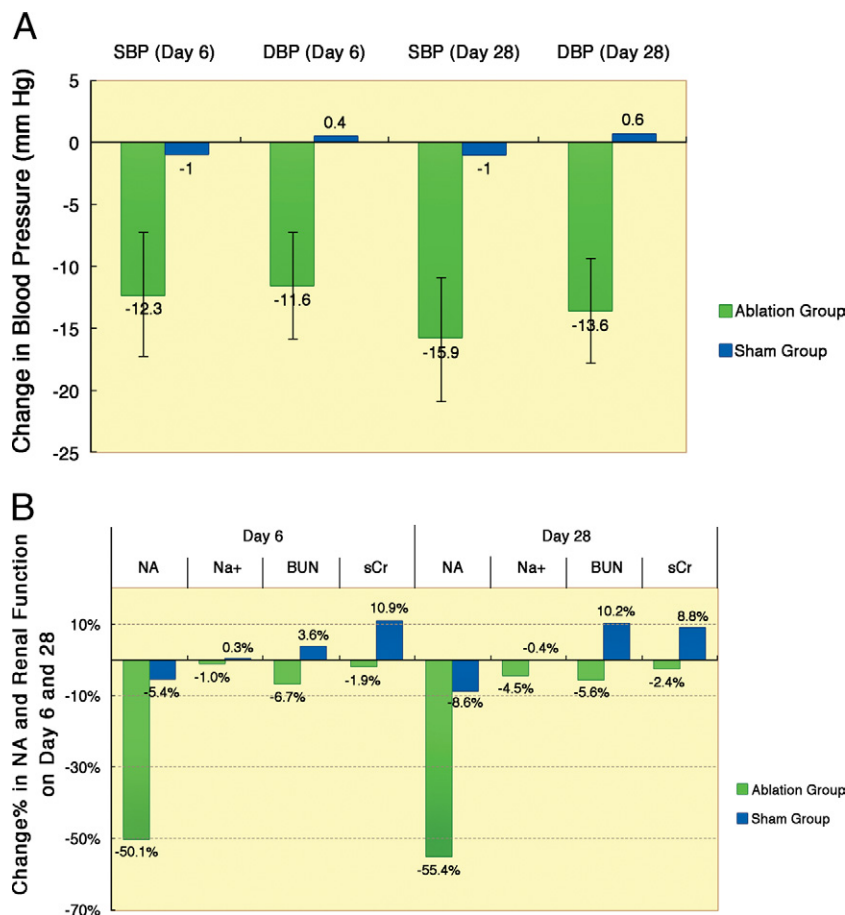


Figure 2 Changes in SBP and DBP on Days 6 and 28 After RSD; Percent Changes in NA, BUN, sCr, and Na⁺ on Days 6 and 28 After Ablation

(A) Blood pressure (BP) was significantly lower compared with baseline values on days 6 and 28 post-ablation in the ablation group; there was no significant change in BP in the sham group. DBP = diastolic BP; RSD = renal sympathetic denervation; SBP = systolic BP. (B) In the ablation group, noradrenaline (NA) was significantly lower on days 6 and 28, and sodium (Na⁺) was lower on day 28 post-ablation compared with baseline values, respectively. There were no significant differences among NA, blood urea nitrogen (BUN), serum creatinine (sCr), and Na⁺ at 6 and 28 days follow-up in the sham group.

the fatty tissue. Bleeding spots, ulcers, and thrombi were not observed on the targeted renal arteries. In addition, histological examination showed an intact vascular structure with an intact endothelium and vascular smooth muscle cells. No evidence of inflammatory cell infiltration, hyperplasia, or stenosis was observed 28 days later.

Discussion

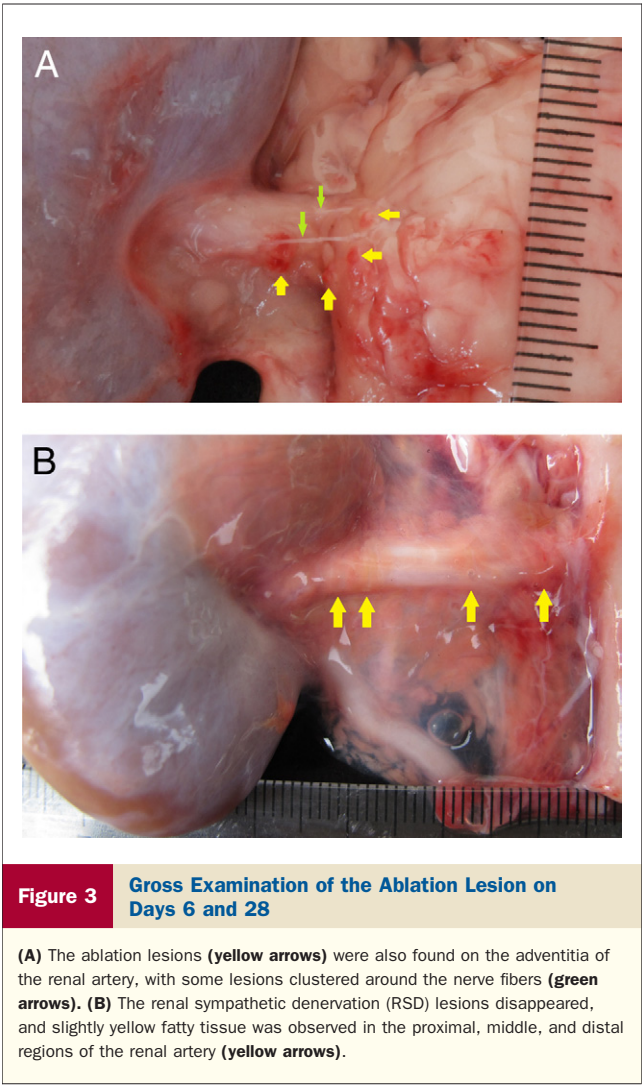
The HIFU technique is a promising strategy for noninvasive deep tissue ablation due to its ability to penetrate and target tissues of interest. The acoustic energy can be delivered to the target region inside the body for therapeutic ablation without significant tissue injury along the path of the acoustic beam and with acceptable targeting accuracy in clinic practice (10,15). In the current study, noninvasive RSD ablation was achieved in every animal by using a clinically approved HIFU apparatus. After properly prepar-

ing the skin by degreasing and degassing, the energy can be more effectively delivered into the target tissues, thus reducing the energy loss and possible tissue injury along the acoustic path. On day 28 post-ablation, both BP and NA were significantly lower than the baseline and the sham group values. Hyperplasia and stenosis of the renal arteries were not found, whereas the disruption of the renal nerve remained, and the myxoid change and shrinkage of renal nerve fibers were more significant, which suggests the RSD persisted. The sham group served to control for factors related to HIFU that could interfere with the results. The results from the sham group demonstrate that our noninvasive approach had little impact on BP or NA.

With the guidance of CDFI, extracorporeal HIFU acoustic energy can easily be targeted to the renal artery. In our dual renal nerve ablation, a mean of 36.3 acoustic emissions were delivered, but the cumulative duration was only approximately 73 s; therefore, the entire procedure duration

Table 1 BP, NA, and Renal Function of the Ablation and Sham Groups at Baseline and Days 6 and 28	Ablation Group (n = 18)									
	Killed at Day 6 (n = 10)					Killed at Day 28 (n = 8)				
	Variable	Baseline	Day 6	p Value*	Baseline	Day 28	p Value*	Baseline	Day 6	Day 28
Sham Group (n = 5)	SBP	124.1 ± 7.3	111.8 ± 7.5	<0.001	128.8 ± 9.4	112.9 ± 8.4	<0.001	125.8 ± 8.3	126.2 ± 8.6	126.4 ± 7.7
	DBP	82.0 ± 9.1	70.4 ± 7.8	<0.001	83.1 ± 10.1	69.5 ± 7.4	<0.001	82.4 ± 7.3	82.2 ± 8.3	83.0 ± 8.4
	NA	582.9 ± 82.3	290.0 ± 41.1	<0.001	587.3 ± 79.5	261.8 ± 67.0	<0.001	596.8 ± 84.1	564.8 ± 80.4	545.4 ± 97.9
	Na ⁺	149.7 ± 4.2	148.3 ± 4.0	0.417	149.3 ± 5.3	142.6 ± 3.1	0.007	149.9 ± 4.5	150.4 ± 3.7	149.3 ± 4.5
	BUN	36.3 ± 0.46	3.38 ± 0.69	0.180	3.68 ± 0.50	3.48 ± 0.73	0.537	3.54 ± 0.36	3.62 ± 0.87	3.90 ± 1.22
	sCr	54.9 ± 8.3	53.9 ± 7.7	0.637	53.6 ± 4.7	52.3 ± 3.7	0.763	53.4 ± 7.5	59.1 ± 5.5	58.0 ± 14.1
	p Value†									
	p Value‡									
	p Value§									

Values are mean ± SD. *Postablation versus baseline. †Ablation group versus sham group at day 6. ‡Ablation group versus sham group at day 28. §Within-group comparisons for the sham group. BUN = blood urea nitrogen; BP = blood pressure; DBP = diastolic BP; NA = noradrenaline; Na⁺ = sodium; SBP = systolic BP; sCr = serum creatinine.



can generally be limited to 0.5 h. Although the size of a single lesion created by HIFU ablation is relatively small, increasing the number of ablations in the renal artery adventitia by using different viewing segments should improve the safety and efficiency of RSD.

It remains controversial whether RSD affects the BP of normotensive animals. Some studies indicated that BP was reduced compared with baseline (16,17). In the current study, BP was significantly decreased in a large, healthy, aggressive animal model, which correlated with a remarkable decrease in plasma NA, suggesting that the sympathetic activity may be at least partially reduced by HIFU ablation. The extent of the decrease in diastolic BP was similar to the decrease in systolic BP. Interestingly, our results differ from those reported by some previous studies, which showed that systolic BP decreased markedly more than diastolic BP (2). One possible reason for this difference may be indirectly attributed to the decreased blood volume and Na⁺ levels caused by the large reduction of NA in our normal BP model after HIFU ablation. Furthermore, our results suggest that the HIFU-mediated RSD may be permanent

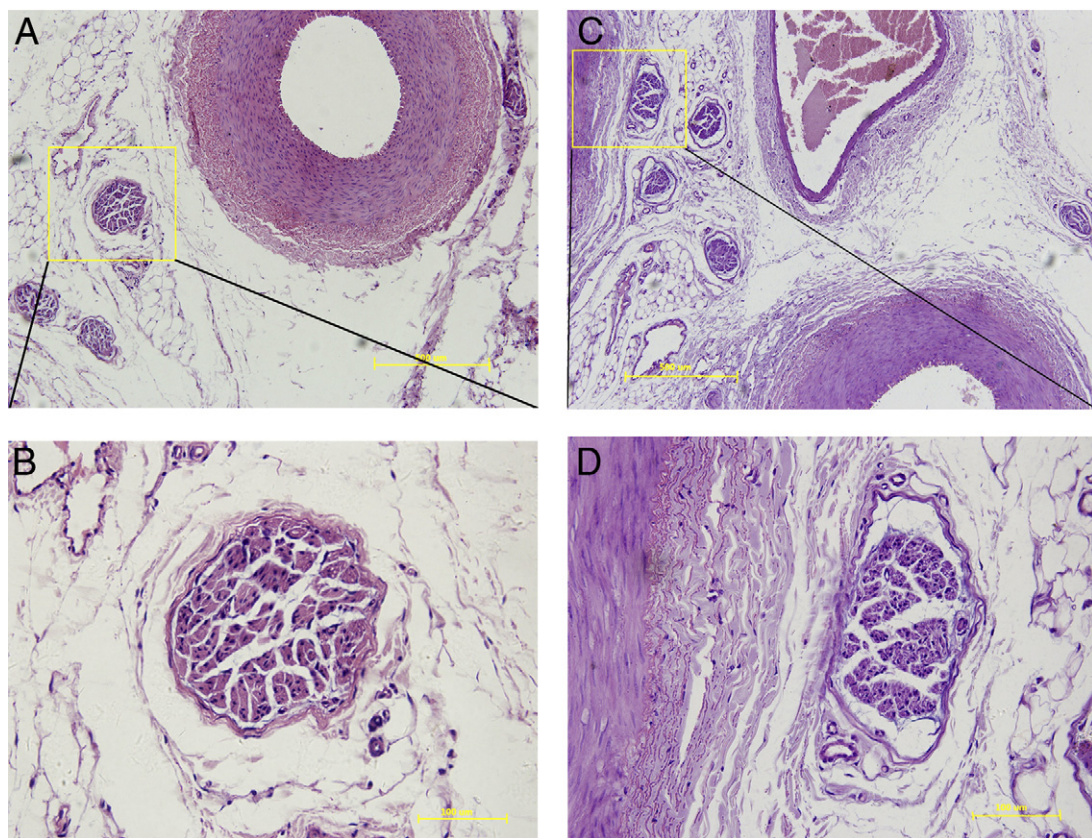


Figure 4 Histological Examination of the Target Nerve Bundles on Days 6 and 28 After RSD

(A) Day 6 after RSD (H&E $\times 100$). The renal artery with an intact wall and endothelium surrounded by the damaged nerve fibers. The spaces between the perineurium increased due to the edema and pyknosis of renal nerve fibers. **(B)** Day 6 after RSD (H&E $\times 400$). The nuclei of Schwann cells are darkly stained and exhibit pyknosis, karyorrhexis, or even disappearance. The mild myxoid change of interstitium can be seen. **(C)** Day 28 after RSD (H&E $\times 100$). The renal artery with intact wall and endothelium was surrounded by the damaged nerve fibers. The nerve fibers were shrunk and more vacuolated, and the Schwann cells appeared to be more necrotic on day 28 after RSD. **(D)** Day 28 after RSD (H&E $\times 400$). The myxoid change in the appearance of the nerve fibers was more distinct on day 28 than on day 6. H&E = hematoxylin and eosin stain; RSD = renal sympathetic denervation.

because the myxoid change and shrinkage of the targeted renal nerve fibers were still present 28 days post-ablation.

Although HIFU acoustic energy targeted whole layers of the renal arteries, a pathological evaluation revealed that both the vascular wall and the endothelial layer remained intact. The therapeutically ablated regions were restricted to the vascular adventitia and the area immediately surrounding the fatty tissue. This phenomenon may be explained by the possible cooling effect of the rapidly circulating bloodstream within the targeted renal arteries and the absence of any catheter to limit the flow of the renal artery. This result is consistent with a previous report that blood vessels are more resistant to acoustic energy (18). On the other hand, ultrasound-inhibited nerve conduction block for pain management and treatment of spasticity has been actively investigated for nearly 50 years; this nerve conduction block can be achieved with lower acoustic energy, suggesting that the nerve fibers may be more sensitive to HIFU energy (19,20). Although the gross and histological appearance of the nerve fibers around the ablation target area was normal,

pathological examination revealed that the nerve fiber structure was significantly damaged and disrupted 28 days post-ablation. This phenomenon suggests that acoustic energy may selectively target the nerve fibers at a lower acoustic intensity level.

In a study of patients with uterine fibroids undergoing HIFU ablation (21) in which the ablative depth was similar to our study, although the incidence of pain was frequent, the pain was described as slight to moderate. With lower energy intensity and very short duration of acoustic delivery, the authors presumed that the pain experienced by patients undergoing HIFU ablation is acceptable.

High acoustic intensity and long-time acoustic energy delivery induced skin toxicity (8/30) and edema (8/30) at the treatment site when HIFU was used for tumor ablation, although most of these adverse effects were slight (10). In our study, the acoustic intensity and exposure were significantly lower than that used in previous studies, and the cumulative acoustic energy used in this study was approximately 3% of that previously used for clinical tumor ablation

(i.e., 250 vs. 399.5 W and 72 vs. 1,200 s) (10,21). In addition, our total procedure time was significantly shorter. Thus, the lower energy input delivered by HIFU may reduce the discomfort and damage caused by the procedure, and this further supports the safety claims of its possible use in RSD in clinical settings.

On the basis of the results of the gross and microscopic examinations, we found no evidence of significant injuries along the acoustic transmission path, such as in the abdominal wall, kidney, and tissues around the target renal arteries. Nonetheless, it is conceivable that mild injuries occurred along the path but quickly healed because the acoustic intensity within these tissues was far lower than that at the focal points.

Unlike the catheter-based strategy, the HIFU-mediated RSD technique can be performed relatively independently of anatomic variations in renal arteries. Thus, this technique may be more suitable for certain conditions, such as bifurcated renal arteries and renal arteries that are smaller and shorter than normal (22). In contrast to the catheter-based strategy, the HIFU technique uses ultrasound without X-irradiation as a guide, which helps avoid radiation exposure to both patients and operators. Furthermore, although the therapeutic region of a single ablation is relatively small, multiple ablation points may be combined to achieve a desirable RSD for individual patients. Mild RSD may be more suitable for individuals with common hypertension and is not limited to those with drug-resistant hypertension.

Study limitations. An invasive BP measurement under anesthesia instead of in the conscious state was performed in this study due to the technical difficulties of the latter. We observed a possible change in BP measured in the conscious state after HIFU, which needs further evaluation. The effect of targeting RSD by using the HIFU technique depended on the acoustic window and required CDFI guidance. Therefore, this new technique may be not suitable for obese patients or patients with emphysema. As an alternative, it may be possible to use HIFU guided by magnetic resonance imaging. Furthermore, a long-term follow-up study is necessary to fully evaluate the efficacy and safety of the HIFU strategy. A clinical trial may provide the most valuable information.

Conclusions

Under CDFI guidance, RSD was achieved in a noninvasive manner in normotensive canines by using the extracorporeal HIFU technique without significant morbidity or mortality. This new strategy may provide an alternative approach for the clinical treatment of drug-resistant hypertension and other conditions associated with sympathetic overactivity.

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Key Words: ablation ■ extracorporeal high-intensity focused ultrasound ■ hypertension ■ noninvasive ■ renal sympathetic denervation.